Centers for Disease Control and Prevention
Epidemiology Program Office
Case Studies in Applied Epidemiology
No. 873-703

An Epidemic of Thyrotoxicosis

Instructor's Guide

Learning Objectives
After completing this case study, the participant should be able to:

- ☐ List the key tasks involved in investigating epidemics of unknown cause;
- ☐ Describe the roles, responsibilities, and relationships of federal versus state public health agencies in a field investigation;
- ☐ Assign appropriate priority to key tasks during an investigation; and
- ☐ Describe jurisdictions of health agencies at various levels of government.

This case study was developed by Frederic Shaw and edited by Richard Dicker in 1987. Current version was revised and updated by Richard Dicker and Julie Magri with input from the 2003 EIS Summer Course instructors.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

PART I

On the afternoon of June 16, 1985, an endocrinologist at the University of South Dakota, Sioux Falls, was examining a patient with recent-onset thyrotoxicosis (manifestations of excess thyroid hormone) when the patient mentioned that there were four other people in his small town with the same problem. The patient was the postmaster of Valley Springs, South Dakota (population 801).

Just a few days earlier, the endocrinologist had read an abstract of a CDC investigation describing an epidemic of painless thyroiditis in York County, Nebraska, in early 1984. Although the cause was never determined, the most likely etiology was believed to be viral infection.

By speaking with other local physicians, the endocrinologist identified seven other patients with possible thyrotoxicosis. Six of the patients lived in Valley Springs, and two lived in southwest Minnesota. All exhibited classic symptoms of thyrotoxicosis (anxiety, shortness of breath, palpitations, rapid heart beat, weight loss), and all had markedly elevated thyroxine (T_4) levels. All but one had abnormally low radioiodine thyroid uptakes. The endocrinologist called CDC and provided the EIS Officer with the information summarized in the line listing below.

Table 1. Line listing of patients with clinical thyrotoxicosis reported to CDC on initial telephone call, June 18, 1985

Patient	Age	Sex	Residence	Onset date	Max. T_4*	24-hr. RAIU (%)†
1	53	M	Valley Springs, S.D.	3-84	>20	0.6
2	34	F	Valley Springs, S.D.	5-85	18	17.0
3	57	M	Beaver Creek, S.D.	5-85	22	1.0
4	41	F	Valley Springs, S.D.	5-85	18	2.6
5	76	F	Valley Springs, S.D.	6-85	14	7.8
6	?	M	Luverne, Minn.	6-85	"high"	1.0
7	29	M	Valley Springs, S.D.	?	27	2.2
8	?	M	Luverne, Minn.	?	"high"	"low"

* Normal range = 5-12.
† RAIU - radioactive iodine uptake; normal range = 10%-35%.

Question 1: Place yourself in the role of the EIS Officer. Can you say that an epidemic exists?

Answer 1
instructor's Note: Do not belabor. This question was addressed in the Washington County case study.

There is an apparent cluster. It is not clear whether it is an outbreak or epidemic, because we don't know the background rate of hyperthyroidism, or whether there have been changes in factors such as diagnostic procedures, reporting procedures, or size of the population.

The following definitions are from *A Dictionary of Epidemiology, Fourth Edition*:

Epidemic – The occurrence in a community or region of cases of an illness, health-related behavior, or other health-related events clearly in excess of normal expectancy.
Outbreak – An epidemic limited to localized increase in the incidence of a disease, e.g., in a village, town, or closed institution.
Cluster – Aggregation of relatively uncommon events or diseases in space and/or time in amounts that are *believed* or *perceived* to be greater than could be expected by chance.

Question 2: What additional information might you try to collect on the phone call?

Answer 2
Instructor's Note: Do not belabor. This question was addressed in the Washington County case study.
Instructor's Tip: Allow students to toss out a few items of information they'd like to collect. You then might suggest that some sort of organization or categorization of the questions might be helpful. One way to organize the questions is to place them into the categories of What (clinical), Who, Where, When (Person, Place, Time), Why (Possible etiologies), and Operational Issues.

Additional questions to ask related to **diagnosis** might include:
- Is the diagnosis of thyrotoxicosis confirmed?
- Is there a laboratory error? (New or change in laboratory technique? Laboratory personnel?)
- Is the physician over diagnosing? (New doctor in town?)

Additional questions to ask related to **time, place, person** might include:
- What is the denominator for the observed cases? (What are the referral patterns? Has the pattern changed?)
- What is the background incidence of thyrotoxicosis--the expected rate in the general population?
- Is the number of observed cases greater than that expected by the background rate?

Additional questions to ask related to **possible etiologies** might include:
- Are the cases related in an obvious way? Do the case-patients know each other? Do they work together? What are their occupations?
- Are there other plausible explanations such as family history or past history of disease?
- Does the endocrinologist (or do the patients themselves) have any hypotheses about the cause?

Additional questions to ask related to **operational issues** might include:
- Has the state epidemiologist been notified? (Call came from private endocrinologist.)
- What has already been done? Who else is already involved?
- How long in practice (new or old-timer)?

Question 3: Which of the following tasks are appropriate next steps to take? Which are not appropriate? Why or why not?

a. Review information with your supervisor in Atlanta.
b. Contact the state epidemiologist in South Dakota.
c. Book an airline flight to Sioux Falls.
d. Contact state health departments in neighboring states.
e. Contact local health departments in areas affected by the outbreak to identify more cases.
f. Contact physicians in communities affected by the outbreak to identify more cases.

Answer 3
The state health department is responsible for health issues in the state. CDC serves as a resource.

Appropriate tasks might be a, b, and then d. It is not appropriate to contact local health departments (that should be done through the state health department), or to contact local physicians (should also be done through the state health department).

Additional discussions involved the EIS Officer, the South Dakota State Epidemiologist, the Director of the South Dakota Department of Health Communicable Disease Program, and CDC staff. The South Dakota State Epidemiologist invited CDC to send a team to investigate the cluster in Valley Springs. Accordingly, the EIS Officer and a medical student departed from Atlanta for Sioux Falls, South Dakota, on June 23 to assist the state health department in an investigation.

On the airplane, the Officer and medical student reviewed the differential diagnosis for thyrotoxicosis, as summarized in Table 2.

Table 2. Causes of Thyrotoxicosis

I. Disorders associated with thyroid hyperfunction (usually associated with increased radioactive iodine uptake.)

   A. Excess production of Thyroid Stimulating Hormone (TSH)
   B. Abnormal thyroid stimulation
      1. Graves' disease
      2. Trophoblastic tumor
   C. Intrinsic thyroid autonomy
      1. Hyperfunctioning adenoma
      2. Toxic multinodular goiter

II. Disorders not associated with thyroid hyperfunction (usually associated with decreased radioactive iodine uptake)

   A. Disorders of hormone storage
      1. Subacute granulomatous thyroiditis
      2. Subacute lymphocytic thyroiditis (painless thyroiditis)
         a. sporadic
         b. postpartum
      3. Chronic thyroiditis with transient thyrotoxicosis
   B. Extrathyroid source of hormone
      1. Thyrotoxicosis factitia
      2. Ectopic thyroid tissue

III. Jod-Basedow disease – iodine-induced hyperthyroidism (usually associated with decreased radioactive iodine uptake)

Note: Jod-Basedow disease is the only form of hyperthyroidism that has been well-documented to occur in epidemic form. However, it has not appeared in the United States in 50 years.

The endocrinologist met the CDC investigators at the airport and gave them additional information about the area. Valley Springs, S.D., is located about 15 miles east of Sioux Falls on Interstate 90. Luverne, Minn. (population 4,568), lies 10 miles to the east of Valley Springs. The economy of the entire area is agricultural and is based on the production of beef cattle. There are no physicians in Valley Springs. Luverne has one medical clinic and a community hospital. Specialty referrals for the entire area are generally made to Sioux Falls.

At this point, the investigative team included the endocrinologist, staff from the South Dakota Health Department, the EIS Officer, and the medical student.

Question 4: Which of the following steps would you take now, and which should wait for later? Explain why.

a. Set up a control program.
b. Set up a case-finding strategy.
c. Generate etiologic hypotheses.
d. Interview the known case-patients.
e. Create a case definition.
f. Perform etiologic epidemiologic studies using the eight case-patients already known.
g. Contact the Minnesota State Epidemiologist regarding the two Minnesota cases.
h. Confirm the diagnosis.

Answer 4

Instructor's Note: Categorize each step as either sooner or later. Do not try to put in rank order. Point out that priorities may vary for different people.

Early steps include:

g. State epidemiologists in states where case-patients reside (i.e., Minnesota) should be notified as a courtesy.

h. Confirm the diagnosis. The Officer need not be an expert endocrine diagnostician, but s/he should determine the reliability of the diagnosis—who has made the diagnosis, and whether it has been confirmed by a knowledgeable specialist, by appropriate laboratory methods, etc.

d. EIS Officer may want to interview known case-patients to generate etiologic hypotheses.

b. Local health officials may want to determine extent of the problem. If the problem extends to large areas of the state, control measures and policy decisions may be different than if the problem is confined to a local area.

Question 5: The state health officials want to proceed by conducting additional case finding, to determine the extent of the problem. Your supervisor wants you to conduct a quick case-control study to try and identify possible etiologies. What do you do?

Answer 5

Approaches might be to:

a. Enlist more help so both could be done.
b. Get both Atlanta supervisor and state health officials on a conference call so strategies can be discussed and lead responsibility determined. This will avoid having you, the EIS Officer, caught in the middle. In general, CDC is invited to participate in an investigation by a state, so the state is in charge. However, states may choose to defer to CDC in investigations.

NOTE: Without a good hypothesis in hand it is probably too early to do a case-control study.

Question 6: Are there any outbreak situations in which setting up a control program would precede further epidemiologic investigations? If yes, give an example.

Answer 6

Control measures may precede further investigation when faced with an outbreak of a disease of known etiology that has severe consequences, and when there is potential for ongoing transmission. Control measures must be available and effective. Examples include vaccine-preventable diseases such as measles and meningitis, and hepatitis A if immunoglobulin is available.

The following table is taken from Goodman RA, Buehler JW, Koplan JP. The epidemiologic field investigation: science and judgment in public health practice. *Am J Epidemiol* 1989:132:9-16.

Relative priority of investigative and control efforts during an outbreak, based on level of knowledge of the source / mode of transmission, and etiologic agent

		SOURCE / MODE OF TRANSMISSION (How people are getting exposed to the pathogen)	
		Known	Unknown
ETIOLOGY (Pathogen)	Known	Investigation + Control +++	Investigation +++ Control +
	Unknown	Investigation +++ Control +++	Investigation +++ Control +

+++ = highest priority
+ = lower priority

Example of Source/Mode Known, Etiology Known (cell A): *E. coli* in hamburger
Example of Source/Mode Unknown, Etiology Known (cell B): salmonellosis and marijuana
Example of Source/Mode Known, Etiology Unknown (cell C): SARS before coronavirus identified
Example of Source Unknown, Etiology Unknown (cell D): Legionnaires' disease in Philadelphia, 1976

The investigators decided to start the investigation by interviewing the eight known case-patients in order to verify the disease process and to look for obvious etiologic clues. They took blood specimens from the case-patients as well as from their family members.

Question 7: Was it appropriate to obtain blood specimens from case-patients and family members at this point in this investigation? Why or why not?

Answer 7

Instructor's Note: Two important themes:

- Informed consent - While this Epi Aid may not need to go through CDC's IRB, one should think about the requirements that might be imposed if it did need to go through the IRB. For example, before drawing blood, you need to get informed consent, and as part of informed consent you'd have to tell the family member why you are drawing blood.
- Laboratory - Discuss with laboratory staff how to collect specimens, how to store them, how to transport them, how much blood to take, and other issues related to specimen collection. It is also appropriate to discuss the need for human subjects review in the states.

A general principle of field epidemiology is "get it while you can." This principle relates to interviews as well as to blood and other specimens. You always have the option of later excluding specimens that may not be appropriate or necessary for particular analyses.

PROS:
- Confirm diagnosis (if possible).
- Detect asymptomatic cases.
- Obtain hard data for studies.
- Etiologic clues such as serology may be used to detect a viral agent.
- This may be your only opportunity to get the specimens.

CONS:
- Time required might be better spent increasing case ascertainment.
- Personnel required to process large number of specimens.
- May reduce cooperation/increase hostility.
- May increase expectations of prompt answers.

The eight interviews produced no valuable etiologic clues. The case-patients were geographically clustered but seemed to have no identifiable common exposures. Blood specimens from case-patients and their family members underwent a variety of tests, including tests for virus-specific antibodies, T_4, free T_4, T_3 resin uptake, and T_3. While waiting for the blood test results, the team decided that the next step should be to increase case ascertainment.

Question 8: What case-finding method(s) might you use?

Answer 8

Instructor's Note: Has been covered previously. Do not belabor.

Case finding might include contacting:

a. Laboratories in the area.
b. Hospitals.
c. Clinics.
d. County health departments.
e. All physicians in the area (letters).
f. All endocrinologists in the area (telephone calls).
g. The media (telephone calls).
h. The case-patients to ask whether they know of any other persons with similar illness.

For case ascertainment, you need to determine what area you are interested in, i.e., a few counties, area of the state, the whole state, and/or neighboring states.

Since radioactive-iodine-uptake scans were performed in only two facilities in the entire area, two hospitals in Sioux Falls, the team decided to begin case ascertainment by reviewing the results of all uptakes done there in the past year. They identified 33 patients with abnormally low uptakes. These patients were clustered around Luverne, Minnesota.

Question 9: How might you proceed?

Answer 9

1. Call the Minnesota State Epidemiologist.
2. Do additional case finding in Minnesota.
3. Contact patients' physicians; review medical charts for etiologic clues.
4. Interview known case-patients.
5. Summarize information and generate hypotheses that could be tested in an analytic study.

PART II

Following discussions with the Minnesota State Epidemiologist, the Minnesota Department of Health joined the investigation. The investigators visited the only source of health care in Luverne, a clinic. The medical director of the clinic stated that he had seen an unusual number of elevated T_4's lately, but said that he had ascribed the phenomenon to laboratory error. Team members reviewed the charts of all clinic patients with elevated T_4's in the past year. They interviewed and obtained blood from all these patients and their families.

Laboratory results from the blood taken from the first 15 case-patients were now available. As expected, all had elevated free T_4's. The team was startled to find, however, that 75% of asymptomatic family members of case-patients also had elevated T_4's.

The total number of case-patients with unexplained thyrotoxicosis was now 28. About five to eight new cases per week were being recognized at the Luverne clinic. Patients' symptoms are shown in Table 3.

Table 3. Distribution of symptoms among patients with thyrotoxicosis, Luverne Clinic, 1985

Major symptom	Percent with symptom	Major symptom	Percent with symptom
Fatigue	92	Nervousness	60
Weakness	83	Sleeplessness	51
Tachycardia or palpitations	79	Headaches	45
Shortness of breath	68	Heat intolerance	38
Weight loss	66	Excessive sweating	34
Tremor	62	Diarrhea	16

The investigators agreed to widen case finding to define the extent of the outbreak. They decided to review patients' records from the medical clinics in five communities in southwestern Minnesota around Luverne, in southeastern South Dakota, and in northwestern Iowa for the previous 18 months. The team also planned to contact by telephone all physicians in eight counties in southwestern Minnesota and question them about the occurrence of thyrotoxicosis among their patients in the past 6 months. In addition, the investigators decided to send letters to all physicians in South Dakota and southwestern Minnesota describing the outbreak and requesting them to report suspected cases to their state health departments.

In order to do this, team members decided that they needed a more formal case definition.

Question 10: Write the case definition that you would now use during widened case surveillance. How might this definition differ from the case definition you might use in a case-control study of the same illness?

Answer 10

Instructor's Note: Split the class into groups of about 4 students.

For case ascertainment you want to use a sensitive case definition that "casts the net wide," capturing most of the true cases and, unfortunately, some non-cases. One could develop "definite" vs. "probable" case definitions. For example:

Person: Any age, exclude thyroid medications and history of thyroid disease.
Place: Southeast South Dakota, southwest Minnesota, northwest Iowa.
Time: January 1, 1984, to present.
Clinical, Definite: a. symptomatic, with ↑T_4, ↑T_3, ↑free T_4, or
b. asymptomatic, with ↑T_4, ↑T_3, ↑free T_4.
Clinical, Possible: ≥3 symptoms, laboratory results pending or unavailable.

For a case-control study you need to minimize misclassification, so you need a more specific case definition, e.g., restrict the study to definite cases with narrower person, place, and time characteristics.

PART III

A case was defined as an illness characterized by the presence of one or more values for T_4, free T_4, or T_3 that were at least 25% higher than the upper limit of normal in the laboratory in which the test was performed, and included two or more of the following symptoms: sleeplessness, nervousness, headache, increased heart rate or palpitations, shortness of breath, fatigue, excessive sweating, tremor, diarrhea, heat intolerance, or weight loss. Patients were excluded if they had Graves' disease or if they had received thyroid hormone-replacement therapy during the 2 months before diagnosis.

Question 11: What are the advantages and disadvantages of this case definition?

Answer 11

Advantages

1. The clinical component is specific, decreasing the likelihood of misclassification of cases in case-control analysis.
2. Laboratory-based definition facilitates case finding through laboratories.

Disadvantages

1. It excludes asymptomatic persons who may have cases.
2. This definition has no time and place specified.
3. This definition will miss case-patients who haven't sought medical attention (this is often true).

Widened surveillance produced additional cases (total N = 121). An age-sex breakdown of cases, an epidemic curve, and an incidence map are shown in Table 4.

Table 4. Age and sex distribution of 121 patients with thyrotoxicosis, Minnesota and South Dakota

Age group (years)	Males	Females	Total No.	Total (%)
0-9	1	1	2	(2)
10-19	3	5	8	(7)
20-29	7	8	15	(12)
30-39	15	14	29	(24)
40-49	8	10	18	(15)
50-59	16	6	22	(18)
60-69	9	5	14	(12)
70+	3	10	13	(11)
Total	62	59	121	(100)

Figure 1. Number of cases of thyrotoxicosis by month of onset of symptoms, Minnesota, South Dakota, and Iowa, February 1984 – August 1985 (n=121)

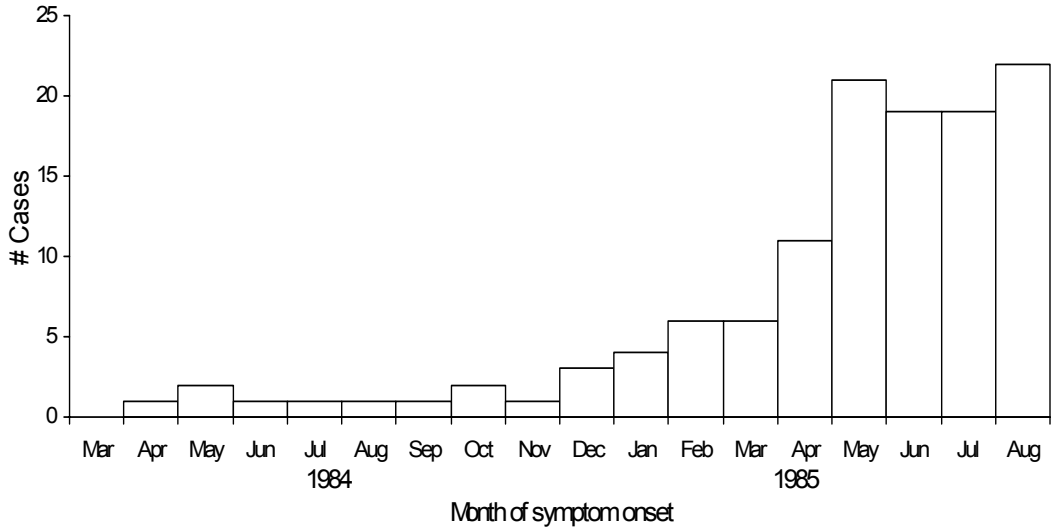


Figure 2. Number of cases of thyrotoxicosis by month of diagnosis, Minnesota, South Dakota, and Iowa, February 1984 – August 1985 (n=121)

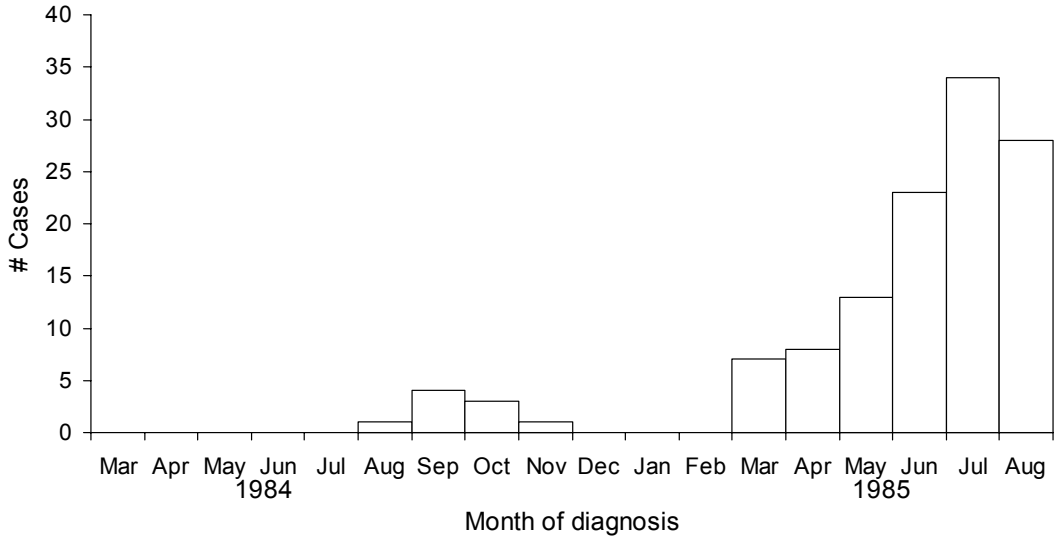
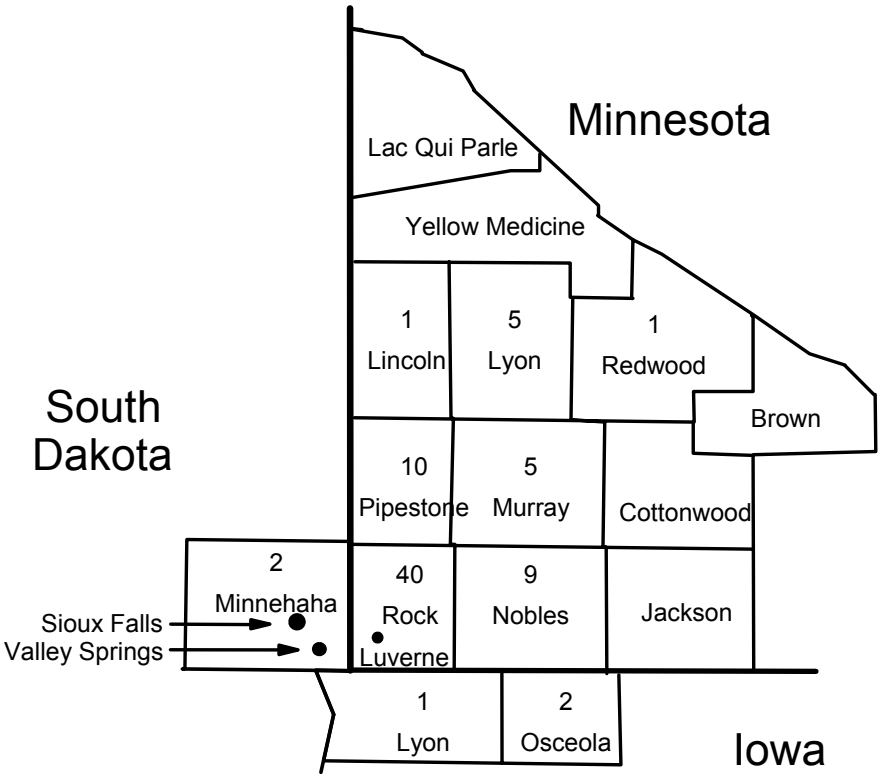


Figure 3. Incidence per 10,000 residents of thyrotoxicosis by county, Minnesota, South Dakota, and Iowa, February 1984 – August 1985



Sitting in a small country-western bar in Sioux Falls late at night in early September, the team members discussed their current hypotheses for the etiology of the outbreak on the basis of all the data accumulated so far. One member took a beer-dampened cocktail napkin and scratched out the major descriptive findings (time, place, person) that he knew about the cases so far.

Question 12: What would you write on the cocktail napkin?

Answer 12
Instructor's Note: Break into groups of about four for this question.
Think in terms of time, place, person:
1. The increase in cases appeared to have begun about December 1984 / January 1985.
2. The epidemic is ongoing.
3. The number of cases seems to be increasing and not yet leveling off.
4. The epidemiology does not suggest classic point source or person-to-person transmission.
5. Cases geographically clustered around Luverne.
6. Fewer cases occur as the distance from Luverne increases.
7. There is an equal distribution of males and females among case-patients.
8. Most patients are 30-59 years of age. Few cases in children. However, because the denominators are unknown, we cannot calculate age-specific incidence rates.

Two nationally recognized thyroid experts were called in to provide consultation to the investigative team. After interviewing and examining several case-patients, they were perplexed by the outbreak but felt that the etiology was probably viral. Several team members favored iodine-induced hyperthyroidism as the most likely etiology; they felt that an accident might have occurred during the routine addition of iodine to flour. (An epidemic of thyrotoxicosis that occurred in Tasmania in the late 1960s was attributed to the addition of potassium iodate to commercially baked bread as a prophylactic measure against goiter.) They decided to conduct an etiologic study as the next logical step.

Question 13: Exactly what type of study would you propose? Why?
a. Additional in-depth interviews with the patients, perhaps as a group, since the investigators have speculations but no hypotheses supported by science, observation, or data.
b. A cross-sectional survey of a population-based sample of households in and around Luverne (questionnaire and blood for thyroid-function studies, iodine levels, and viral serology).
c. A retrospective cohort study. For example, define exposure as exposure to baked products that could contain toxic levels of iodine additives.
d. A prospective cohort study. For example, define exposure as exposure to baked products that could contain toxic levels of iodine additives.
e. A case-control study. For example, case-patients and control subjects would be asked about exposure to baked products and other foods which could contain toxic levels of iodine additives.
f. Random testing of all foods and liquids found in case-patients' kitchens for iodine levels and viral cultures.

Answer 13
In-depth interviews might be warranted. However, if a study is going to be done, case-control study would be the study of choice. At this point, we want to include cases with a known outcome (hyperthyroidism) to determine possible exposures (etiology). We cannot do a cohort study since the exposure is unknown (who would be enrolled in the study?)

Random testing of products in the kitchen would be possible but probably not worth the effort. In addition, this assumes consumption of exogenous iodine or thyroid hormone as the etiology of the outbreak.

A cross-sectional survey is possible but would be more time consuming and expensive than a case-control study, and would probably not yield any more or better information.

PART IV

The investigators decided to carry out a case-control study. Case-patients were selected for the study if their illnesses fulfilled the case definition and if they had experienced the onset of symptoms in the previous six months. In households with more than one patient, only the family member with the earliest onset of symptoms was included in the study. The first 44 patients who met these criteria were enrolled.

Question 14: Do you agree with the decision to include only the earliest affected family member? Why or why not?

Answer 14

Again this issue falls under the general principle of field epidemiology of "get it while you can." In this particular investigation, other family members could be interviewed while you're there – they can always be excluded later in the analysis if appropriate.

If you are primarily interested in risk factors for introduction of disease into the household, only the first affected family member should be included. Chi-square analysis of a case-control study assumes independence of the case-patients in terms of exposures. Since members of a family usually eat similar foods and may have other similar exposures, including all family members who are case-patients might provide spurious results.

If you wish to study person-to-person transmission (i.e., an infectious etiology), you would want to look at secondary attack rates, and you would need information on the "secondary" cases.

If you think that all family members are "co-primaries," then could pick randomly. In fact more recent cases might have better recall than cases that occurred months ago.

Question 15: Whom might you select as controls?

Answer 15

Instructors note: Focus on two issues:
a. Source of controls.
b. Inclusion of asymptomatic case-patients in the control group.

- In view of the high prevalence of asymptomatic persons in the community, it would be desirable to be sure that controls are not asymptomatic persons with elevated T_4's, since their inclusion would bias the results toward the null.
- Random neighborhood controls may have similar risk of exposure as case-patients (same geographic location, same socioeconomic status).
- Clinic controls may facilitate collection of blood from controls because the investigator might be able to use samples collected for other purposes, or at least at the same time. However, the clinic may serve a different population from just the area of residence.
- Friend controls may have similar preferences as case-patients and therefore obscure an association.
- Workplace controls. Could limit study to adults.

Question 16: What exposures would you ask about in the study?

Answer 16
Instructor's Note #1: Split the class into groups.

Instructor's Note #2: Information included on the questionnaire should be based on the hypotheses to be tested, plus possible modifiers. At this point, the investigators had few solid hypotheses, and may have been going on a fishing expedition. (What are you going to ask if you don't know what you are looking for?) This is poor practice. Without solid hypotheses to test, the investigators might have been better off "milking the cases," for example, gathering those that did not know each other into discussion where they can brainstorm and perhaps identify previously overlooked exposures they have in common.

- Specific food consumption at time of onset; if not possible, food preferences
- Usual food store
- Source of salt, flour
- "Unusual" foods, e.g., health foods, supplements, etc.
- Water source: municipal, well
- Medications, traditional remedies
- Occupation and place of work
- Animal exposures; pets
- Antecedent viral infection or other illness
- Contact with other known case-patients
- Social gatherings, school, church, clubs, etc
- Travel

PART V

Control subjects for the case-control study were randomly selected from local telephone directories and were matched to case-patients according to the following criteria: the same sex and telephone exchange, and age within 10 years of the corresponding patient if the patient was 30 years of age or older, and within 5 years if the patient was under 30 years of age.

Just as the case-control study was getting under way, a new case-patient was diagnosed in Sioux Falls and was interviewed by some members of the investigative team. The woman, age 25, clearly had painless thyroiditis and hyperthyroidism. She lived in Sioux Falls but frequently visited a grocery store in Valley Springs, S.D., which her father owned. She sometimes purchased groceries there. Team members went to the store and interviewed the proprietor. All goods in the store were obtained from national distribution systems except two – chicken eggs and beef trimmings. The beef trimmings were obtained from a plant near Luverne. Some team members began to suspect that ingestion of beef may have been the source of the outbreak. They hypothesized that iodine contaminated the beef trimmings during processing, where it may have been used as a disinfectant.

Then, during the case-control study, one investigator visited a family of four people where all members of the family except one had illness fulfilling the case definition. The one unaffected member was a young boy who was a vegetarian. The family obtained its meat from the Luverne beef plant.

The results of the case-control study became available. The study showed that two factors were associated with illness – consumption of commercially processed chicken (odds ratio 2.3, p=0.03) and consumption of ground beef prepared by the Luverne plant (odds ratio 1.9, p=0.05). However, during the study, case-patients were not asked about the source of their beef in a uniform way; some team members suspected information bias.

Question 17: How would you obtain further data to test the hypothesis that ingestion of beef or poultry is the cause of the outbreak?

Answer 17

- Do a case-control study.
- Consider visiting the plant to get samples, determine supply lines, watch processing, etc. However, consider when to visit the plant - you will probably want to visit the plant only once, when you have a good idea about what you are looking for, and get all the samples and interviews you can that one time. (By the second visit, the processes may have been cleaned up and answers "sanitized.") Also, you should be accompanied by someone who knows what to look for.
- Another option is to get samples of beef from case-patients' freezers, if available.

PART VI

The investigators decided to conduct a second case-control study to rule out any effect of information bias on the first case-control study and to obtain more information on specific exposures such as type of beef (hamburger, steak, roast) usually consumed and source of beef. The chicken was not implicated in the second study. Some of the results of the second case-control study are shown in Table 5.

Table 5. Matched-pair odds ratios for thyrotoxicosis and meat consumption

Factor	Matched-pair odds ratio
Ate hamburger from Plant A beef trim	23.0
Ate hamburger from privately slaughtered beef	0.08
Ate roast beef from Plant A	0.8
Ate roast beef from privately slaughtered beef	0.4
Ate steak from Plant A	0.9
Ate steak from privately slaughtered beef	0.6

Question 18: Interpret these results. How would you interpret the odds ratio of 0.08 for eating hamburger from privately slaughtered beef?

Answer 18

Consumption of Plant A beef trim is strongly associated with illness. On the other hand, an odds ratio of 0.08 indicates that persons who ate privately slaughtered beef were at sharply decreased risk of becoming ill. If it were biologically plausible, the odds ratio could be interpreted to indicate that privately slaughtered beef protected against illness. Presumably, these people were protected from illness because they were less likely to eat beef slaughtered at Plant A.

Question 19: What elements of causality, if any, were missing from the hamburger-thyrotoxicosis association at this point?

Answer 19

An odds ratio of 23 indicates a strong association with consumption of hamburger from trimmings at Plant A. However, we still don't know what in the beef is causing the hyperthyroidism. Is it iodine? Is it thyroid hormone? Is it an infectious agent? In addition to testing the hamburger, you may want to determine whether case-patients who stop eating the hamburger improve.

Elements of Causality	Met?
Strength of association	Yes
Biologic plausibility	Don't know
Exposure precedes illness	Don't know
Dose-response relationship	Don't know
Consistency among studies	Don't know (2 studies, but same population, and very different magnitudes of effect)

Question 20: What would be your recommendation regarding the beef plant now?

Answer 20
You still do not have enough evidence to close down the plant. If you close it, you may never be able to pinpoint the exact cause. As a result, it may be difficult to know when the problem has been corrected so the plant can be re-opened. Rather than closing the plant, you should observe the processes while they are in operation, such as how the beef trimmings are prepared. You may want to recall beef trimmings that are on the market and alert the public (through the media) not to eat beef trimmings from Plant A.

Question 21: In this setting, describe the jurisdictions and responsibilities of:
a. the State Epidemiologist.
b. the State Veterinarian.
c. CDC.
d. the United States Department of Agriculture.
e. the Food and Drug Administration.

Answer 21
a. The state epidemiologist: Responsibility involves the health and welfare of the people residing in the state. This would include the spread of zoonoses or animal disease to humans, and human disease related to animal products. Although powers vary by state, state epidemiologists could require a plant to close down if its operation posed a threat to the health of state residents.

b. The state veterinarian: Many states have a state veterinarian in the department of agriculture, and a state public health veterinarian in the department of health. In most states, responsibilities of the state veterinarian primarily involves diseased animals in the state. This would include, for example, rabid animals with no human exposure. In the case of this outbreak, no animal disease was identified, so the state veterinarian would have little or no responsibility. However, in some states, the powers of the state veterinarian are broader. In contrast, the state public health veterinarian works with the state epidemiologist and staff on zoonoses, vector-borne diseases, and other animal-related diseases that pose a potential risk to humans.

c. CDC: Responsibility involves responding to requests for epidemiologic or public health aid by states. CDC cannot initiate epidemiologic investigations in states unless invited by the states, but CDC sometimes asks to be invited (state can decline to do so).

d. The United States Department of Agriculture: Responsibility involves monitoring the production of meat and poultry products from the farm to the slaughter house to distribution on the market. This agency is particularly responsible for monitoring interstate commerce involving meat and poultry products.

e. The Food and Drug Administration: Responsibility involves monitoring dairy products and foods that are processed.

Instructor's Note: The lines of authority between USDA and FDA are sometimes difficult to know. For example, USDA regulates corn dogs, FDA regulates bagel dogs. USDA oversees open-face meat sandwiches, FDA oversees closed meat sandwiches. USDA covers pizza with meat topping, FDA covers cheese pizza.

PART VII - CONCLUSION

Investigators went to the Luverne plant. The following is excerpted from a report of the plant investigation:

"Two work shifts per day operated at Plant A, and approximately 800 animals were slaughtered and dressed during each shift. Before April 1983, thyroid glands were selectively removed and sold for use in the manufacture of thyroid extract. After that time, 'gullet trimming' was employed to harvest muscle from the bovine larynx. In this procedure, the larynx was placed vertically on a peg 1 meter above the floor. The sternothyroid and sternohyoid muscles were removed from the larynx with a downward slicing motion... This motion allowed portions of both lobes of the thyroid gland to be inadvertently included in the muscle trimming... Although the process of gullet trimming was performed by a limited number of employees, the presence of thyroid tissue in the neck trimmings could not be attributed to any one employee.

"...Among the 22 boxes of beef trimmings produced before the recall that were examined, thyroid tissue was found in all....No thyroid tissue was found in four boxes produced after gullet trimming was discontinued.

"When samples of the implicated beef were fed to volunteers, significant elevations of T_4 and T_3 occurred.

"On August 29, 1985, because of this investigation, the USDA issued a nationwide advisory that temporarily prohibited gullet trimming in all USDA-inspected plants that slaughter beef and pork."

That prohibition was later made permanent.

Reference

Hedberg CW, Fishbein DB, Janssen RS, Meyers B, et al. An outbreak of thyrotoxicosis caused by the consumption of bovine thyroid gland in ground beef. *N Engl J Med* 1987;316:993-8.